REMARKS

The invention

The present invention relates to expression vectors encoding recombinant, single chain, MHC class II heterodimers that associate with an antigenic peptide and presenting the peptide to a T cell receptor. The MHC class II complexes comprise α and β chains of the MHC class II molecule covalently linked to each other via an amino acid linker comprising the amino acid sequence as set forth in SEQ ID NO: 36. The MHC class II complexes also comprise an antigenic peptide covalently linked to the MHC class II heterodimer portion of the complex via an amino acid linker of 5 to 25 amino acids. In these complexes, the antigenic peptide binds to the antigen binding pocket of the MHC class II component and is specifically recognized by the target T-cell. These single-chain MHC II:peptide complexes can be used, *e.g.*, to treat autoimmune diseases.

Status of the Claims

After entry of this amendment, claims 39, 41-42, 44-46 and 50-54 are pending. Claims 27-38, 40, 43, and 47-49 have been canceled without prejudice to future prosecution. Claims 39, and 44-45 have been amended. New claims 50-54 have been added.

More particularly, claim 39 has been amended to recite a "flexible linker of 5 to 25 amino acids and connecting in-frame the first and second nucleic acid segments; wherein said flexible linker comprises the amino acid sequence GGGGSGGGGSGGGGS (SEQ ID NO: 36)," "wherein linkage of the first DNA segment to the second DNA segment results in a fused first, linker and second DNA polysegment that is capable of expressing a soluble fused, MHC class II heterodimer," "a third nucleic acid segment encoding an antigenic peptide capable of associating with the peptide binding groove of the MHC class II molecule; and a second linker nucleic acid segment encoding a flexible linker of 5 to 25 amino acids and connecting in-frame the third nucleic acid segment to the fused first nucleic acid -first linker-second nucleic acid polysegment; wherein linkage of the third nucleic acid segment to the fused first nucleic acid-first linker-second nucleic acid polysegment results in expression of a soluble fused MHC class II

heterodimer:peptide complex," and to incorporate the recitations of claim 40. Support for this amendment is found in, *e.g.*, claim 40; and in the specification at, *e.g.*, page 6, lines 18 to page 7, line 3; page 9, lines 13-20; and page 108, line 19. Claim 44 has been amended to recite particular linker sequences, *i.e.*, the sequences corresponding to SEQ ID NOS:30 and 31. Support for these amendments is found in the specification at , *e.g.* page 106, line 9 and line 18. Claim 45 has been amended solely to ensure proper dependency. Thus, no new matter is added by any of these amendments.

New claims 50-53 are directed to additional embodiments of the invention. More particularly, claim 50 is directed to expression cassettes encoding particular MHC class II domains. Support for these claims is found in the specification at, *e.g.*, as filed (*see, e.g.*, page 5, lines 11-17 and page 8, line 32 to page 9, line 12. Claims 51-53 are directed to expression cassettes encoding MHC class II heterodimer:peptide complexes comprising particular antigenic peptides. Support for these claims in found in claim 49 and in the specification at, *e.g.*, page 5, lines 29-33 and page 12, lines 7-23. Claim 54 is directed to soluble fused MHC class II heterodimer:peptide complexes that induce anergy in T cells. Support for this claim is found in the specification at, *e.g.*, page 23, lines 13-16. Thus, no new matter is added by new claims 50-54

Request for Substitute Sequence Listing Under 37 C.F.R. §§1.821-1.825

The Examiner has noted that sequences are disclosed in the specification and in the claims that require a SEQ ID NO: Tag (*e.g.*, claims 43 and 44; page 49, line 16; page 56, line 8; Table 3; and Table 4). Applicants have amended claims 43 and 44 so that all of the sequences listed therein are identified with a proper SEQ ID NO: Tag. Applicants also note that the relevant portions of the specification were previously amended to recite proper SEQ ID NO: Tags on February 20, 2002, the filing date of the instant application.

The Examiner has required that Applicants submit a substitute diskette and paper copy of the sequence listing to ensure that the sequence listing on file contains all of the sequences referred to in the specification and claims. Applicant respectfully submit that the diskette and paper copy of the sequence listing provided on February 20, 2002 contains each of

the sequences listed in claims 43 and 44; page 49, line 16; page 56, line 8; Table 3 and Table 4, and is therefore in full compliance with 37 C.F.R. §§1.821-1.825.

A copy of the return postcard indicating that the amendments and sequence listing discussed above were filed on February 20, 2002 is attached as Appendix A. Accordingly, Applicants respectfully request withdrawal of this requirement.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 43 and 44 are rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. Claim 43 has been canceled and claim 44 has been amended as requested by the Examiner to clarify SEQ ID NO: Tag of the sequences recited in the claims. Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

Rejections Under 35 U.S.C. § 102(e)

The claims are rejected under 35 U.S.C. § 102(e). For a rejection of claims under § 102(e) to be properly founded, the Examiner must establish that a single prior art reference discloses each and every element of the claimed invention. See, *e.g.*, *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). In *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991), the Federal Circuit held:

> [A]nticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . .There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010. Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features or limitations of the presently claimed invention.

1. Rejection of claims 39 and 47 as allegedly anticipated by Clark *et al.* (U.S. Patent No. 5,284,935)

Claims 39 and 47 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Clark *et al.* (U.S. Patent No. 5,284,935). Applicants respectfully traverse this rejection.

Clark *et al.* describes a genus of recombinant and naturally occurring MHC complexes, including complexes in which the α and β chains are linked as described by the Examiner. Although the MHC complexes described by Clark *et al.* dominate the present invention, Applicants respectfully assert that the present invention is a separately patentable subgenus invention, as Clark *et al.* does not disclose linking the α and β chains of the complex using the specific linker sequence now recited in the amended claims, *i.e.*, SEQ ID NO:36.

Thus, as explained above and as acknowledged by the Examiner (*see*, Office Action, page 6), the presently claimed invention is not anticipated by the disclosure of Clark *et al.* Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(e) be withdrawn.

2. Rejection of claims 39, 41-42, and 46-47 as allegedly anticipated by Mottez *et al.* (U.S. Patent No. 5,976,551), as evidenced by Madsen *et al.*, *Nat. Genetics* 23(3):343-7 (1999).

Claims 39, 41-42, and 46-47 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Mottez *et al.* (U.S. Patent No. 5,976,551), as evidenced by Madsen *et al.*, *Nat. Genetics* 23(3):343-7 (1999). Applicants respectfully traverse this rejection.

Mottez *et al.* describe MHC molecules in which the domains are covalently linked to form a construct comprising the β2-α2-α1-β1 domains linked in sequence (*see*, *e.g.*, abstract). The β2 and α2 domains of the construct are linker by a first spacer and the α1 and β1 domains are linked by a second spacer (*see*, *e.g.*, Figure 4(b)).

In contrast to Mottez *et al.*, the presently claimed MHC class II heterodimer:peptide complexes are linked in the following order:
β1β2 domain - first linker (SEQ ID NO:36) -α1α2 domain - second linker-peptide.
Moreover, Mottez *et al.* does not disclose linking the domains of an MHC class II molecule with the specific linker sequence recited in the present claims, *i.e.*, SEQ ID NO:36.

Thus, as explained above and as acknowledged by the Examiner (*see*, Office Action, page 6), the presently claimed invention is not anticipated by the disclosure of Mottez *et*

al. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(e) be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

The claims are rejected under 35 U.S.C. § 103(a) over a number of different references. Each of these rejections is addressed below in the order presented by the Examiner.

To establish a prima facie case of obviousness, (1) there must be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. (See, M.P.E.P., § 2143, citing In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

1. Rejection of claims 39 and 41-42 over Clark *et al.* or Mottez *et al.* in view of Strominger *et al.* (U.S. Patent No. 5,874,531), and in view of Fugger *et al.*, PNAS *USA* 91:6151-6155 (1994)

Claims 39 and 41-42 stand rejected over Clark *et al.* or Mottez *et al.* in view of Strominger *et al.* (U.S. Patent No. 5,874,531), and in view of Fugger *et al.*, PNAS *USA* 91:6151-6155 (1994). Applicants respectfully traverse this rejection.

As discussed in detail above, the present invention is a selection invention, *i.e.*, a separately patentably subgenus of MHC class II complexes. As recited in the claims, the α and the β chains of the MHC class II portion of the complex are linked via a linker comprising the sequence set forth in SEQ ID NO:36.

Applicants respectfully assert that one of skill in the art would have had no motivation to combine the cited references to make the MHC class II complex recited in the present claims. A combination of the cited references would not lead to the presently claimed MHC class II complexes linked via a linker comprising the sequence set forth in SEQ ID NO:36.

As explained above, neither Clark *et al.* nor Mottez *et al.* disclose or suggest linking the α and β chains of an MHC class II complex using the specific linker sequence now recited in the amended claims, *i.e.*, SEQ ID NO:36.

Furthermore, neither Strominger *et al.* nor Fugger *et al.* disclose or suggest a linker comprising the sequence set forth in SEQ ID NO:36. Strominger *et al.* discloses self and non-self polypeptides that are implicated in autoimmune disease and concludes that the polypeptides can be used to identify the amino acid motifs of polypeptides involved in autoimmune diseases. There is no suggestion or mention in Strominger of linking the α and β chains of an MHC class II molecule using the specific linker recited in the present claims. Thus, one of skill in the art would have no motivation to combine the disclosures of Clark *et al.* or Mottez *et al.* with the disclosure of Strominger *et al.*

Fugger *et al.* discloses that transgenic mice expressing MHC class II complexes comprising HLA-DRA*0101 and HLA-DRβ1****0401*** and human CD4 can be used to test the antigen presentation capabilities of the HLA-DRA*0101/HLA-DRβ1****0401*** heterodimer, *i.e.*, to characterize all of the peptides that bind to the heterodimer (*see e.g.*, abstract and page 6154, col. 2, last full paragraph). There is no suggestion or mention in Fugger *et al.* of linking the α and β chains of the MHC class II molecule using the specific linker recited in the present claims. Thus, one of skill in the art would have no motivation to combine the disclosures of Clark *et al.* or Mottez *et al.* with the disclosure of Strominger *et al.* and the disclosure of Fugger *et al.*

Therefore, even if one of skill in the art were motivated to combine cited references, the combination would not lead to the presently claimed invention, *i.e.*, an MHC class II complex wherein the α and β chains of the MHC class II portion of the complex are linked via a linker comprising SEQ ID NO:36, because none of the references disclose or suggest the specific linker recited in the present claims. In view of the foregoing, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103.

2. Rejection of claims 39-40, 45, and 48 over Clark *et al.* or Mottez *et al.*, in view of Kappler *et al.* (U.S. Patent No. 5,820,866)

Claims 39-40, 45, and 48 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Clark *et al.* or Mottez *et al.*, in view of Kappler *et al.* (U.S. Patent No. 5,820,866). Applicants respectfully traverse this rejection.

The present invention is a selection invention directed to a separately patentable subgenus of MHC class II complexes, wherein the α and β chains of the complex are linked via a linker comprising SEQ ID NO:36. One of skill in the art would have had no motivation combine the cited references to make the MHC class II complex recited in the present claims.

As explained above, neither Clark *et al.* nor Mottez *et al.* disclose or suggest the linking the α and β chains of and MHC class II complex using the specific linker recited in the present claims.

Kappler *et al.* also does not disclose or suggest using a linker comprising the sequence set forth in SEQ ID NO:36. Kappler *et al.* describe a peptide covalently linked to a MHC class II complex. In contrast to the presently claimed invention, the α1 and β1 chains of the MHC complex described in Kappler *et al.* are ***not*** linked, covalently or otherwise. Thus, one of skill in the art would have no motivation to combine the disclosures of Clark *et al.* or Mottez *et al.* with the disclosure of Kappler *et al.*

Therefore, even if one of skill in the art were motivated to combine cited references, the combination would not lead to the presently claimed invention, *i.e.*, an MHC class II complex wherein the α and β chains of the complex are linked via a linker comprising SEQ ID NO:36, because none of the references disclose or suggest the specific linker recited in the present claims. Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103.

3. Rejection of claims 39, 40, and 49 over Clark *et al.* or Mottez *et al.*, in view of Kappler *et al.*, and further in view of Strominger *et al.* (U.S. Patent No. 5,874,531)

Claims 39-40, 45, and 48 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Clark *et al.* or Mottez *et al.*, in view of Kappler *et al.*, and further in view of Strominger *et al.* Applicants respectfully traverse this rejection.

The present invention is a selection invention directed to a separately patentable subgenus of MHC class II complexes, wherein the α and β chains of the complex are linked via a linker comprising SEQ ID NO:36. One of skill in the art would not have been motivated to combine the cited references to make the MHC class II complex recited in the present claims.

As discussed in detail above, neither Clark *et al.* nor Mottez *et al.* disclose or suggest linking the α and β chains of an MHC class II complex using the specific linker sequence recited in the present claims. In addition, Mottez *et al.* does not disclose or suggest an MHC class II heterodimer:peptide complex with components linked in the order recited in the present claims. Similarly, Kappler *et al.* nor Strominger *et al.* contain a teaching or suggestion in of linking the α1 and β1 chains of an MHC complex using the specific linker recited in the present claims. Thus, one of skill in the art would have no motivation to combine the disclosures of Clark *et al.* or Mottez *et al.* with the disclosure of Kappler *et al.* and Strominger *et al.*

Therefore, even if one of skill in the art were to motivated combine cited references, the combination would not lead to the presently claimed invention, *i.e.*, an MHC class II complex wherein the α and β chains of the complex are linked via a linker comprising SEQ ID NO:36, because none of the references disclose or suggest the specific linker recited in the present claims. Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,

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